Notes for the Practical lesson in Internal Medicine

Chronic insufficiency of adrenal glands (1)

Hyperfunction of adrenal glands (hyperedosteronism and hypercortisolism) (2)

Acute insufficiency of adrenal glands (acute adrenal crisis) (3)

Hormonally active adrenal tumors (4)

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Plan of the Notes

- Anatomy and physiology of adrenal glands: brief summary
- Chronic insufficiency of adrenal glands (1)
  - Hyperfunction of adrenal glands (hypercortisolism) (2)
- Acute insufficiency of adrenal glands (acute adrenal crisis) (3)
- Hormonally active adrenal tumors (4)
- Clinical Endocrinology’ Tests
- Recommended literature
The adrenal gland

- Adrenal glands
- Kidney
- Inferior phrenic arteries
- Right superior suprarenal arteries
- Right middle suprarenal artery
- Right inferior suprarenal artery
- Right renal artery
- Right renal vein
- LEFT ADRENAL GLAND
- Celiac trunk
- Superior mesenteric artery
- Inferior vena cava
- Left renal artery
- Left renal vein
- Left middle suprarenal artery
- Left inferior suprarenal artery
- Left renal artery
- Left renal vein

Figure 18-15a Principles of Anatomy and Physiology, 11/e © 2006 John Wiley & Sons
Anatomy and physiology of adrenal glands

Adrenal cortex produces three major classes of steroids

- all derived from cholesterol
  - mineralocorticoids (aldosterone) from zona glomerulosa (outermost layer = “salt”)
  - glucocorticoids (cortisol) from zona fasciculata (middle layer = “sugar”)
  - androgens from zona reticularis (innermost layer = “sex”)
Anatomy and physiology of adrenal glands

What effects of glucocorticoids do you know?

How are they regulated?
Anatomy and physiology of adrenal glands: effects of GCSs

- stimulate hepatic glucose production (gluconeogenesis)
- increase insulin resistance in peripheral tissues
- increase protein catabolism
- cause leukocytosis and lymphopenia
- inhibit bone formation; stimulate bone resorption
- inhibit fibroblasts, causing collagen and connective tissue loss
- suppress inflammation; impair cell-mediated immunity
- regulate extracellular fluid volume; promote renal solute-free water clearance
Anatomy and physiology of adrenal glands: secretion of GCSs is regulated by ACTH

- diurnal variation of ACTH (higher in a.m. than p.m., with peak around 02.00 hours)
- inhibition of both ACTH and CRH release (negative feedback)
- stress (e.g. fever, pain, hypoglycemia), in addition to stimulating ACTH release, directly stimulates CRH release, over-riding diurnal variation and negative feedback
- 10% free in plasma, 90% bound to transcortin (inactive)
Anatomy and physiology of adrenal glands

What effects of mineralocorticoids do you know?
How are they regulated?
Anatomy and physiology of adrenal glands: aldosterone

- regulates extracellular fluid (ECF) volume through Na+ retention and K+ excretion (by stimulation of distal tubule Na+/K+ ATPase)
Anatomy and physiology of adrenal glands

- **Mineralocorticoid** (aldosterone 100–150 mcg/day) synthesis occurs in zona glomerulosa predominantly under the control of the renin–angiotensin system, although ACTH also contributes to its regulation
  - aldosterone regulated principally by the renin-angiotensin-aldosterone system
  - negative feedback to juxtaglomerular apparatus by long loop (aldosterone via volume expansion) and short loop (angiotensin II via peripheral vasoconstriction)
Anatomy and physiology of adrenal glands

What effects of androgens do you know?

How are they regulated?
Anatomy and physiology of adrenal glands

- **Adrenal gland** (zona reticularis and zona fasciculata) also produces sex steroids, in the form of dehydroepiandrosterone (DHEA), androstenedione and 11-hydroxyandrosterone.
  - peak concentrations in puberty
  - proportion of total androgens (adrenal to gonadal) increases in old age
  - primarily responsible for adrenarche (pubic and axillary hair)
  - adrenal androgen formation is regulated by ACTH (not LH)
Anatomy and physiology of adrenal glands

- Urinary steroid profiling provides quantitative information on the biosynthetic and catabolic pathways

Profiling can be useful in the following:

- Mineralocorticoid hypertension
- Polycystic ovary syndrome
- Congenital adrenal hyperplasia
- Steroid-producing tumors
- Precocious puberty and virilization
- Hirsutism
1) Chronic insufficiency of adrenal glands
1) Chronic insufficiency of adrenal glands:

Primary (Addison’s Disease)

- rare form of adrenal pathology
- most cases are idiopathic
  - likely autoimmune destruction of adrenals (50% of patients)
  - have circulating adrenal antibodies
  - high association with other autoimmune diseases (e.g. chronic lymphocytic thyroiditis,
  - type 1 DM, vitiligo, pernicious anemia)
- metastatic tumour - second commonest cause
1) Chronic insufficiency of adrenal glands:

Primary (Addison’s Disease) (cont’d)

- hemorrhagic infarction - coagulopathy in adults or Waterhouse-Friderichsen syndrome in children (meningococcal or Pseudomonas septicemia)
- adrenalectomy
- granulomatous disease (e.g. TB, sarcoidosis)
- infection - particularly AIDS
1) Chronic insufficiency of adrenal glands:

**Secondary**

- inadequate pituitary ACTH secretion
- multiple etiologies (Hypopituitarism), including withdrawal of
- exogenous steroids that have suppressed pituitary ACTH production
1) Chronic insufficiency of adrenal glands: Clinical Features

**both primary and secondary**
- weakness and fatigue
- postural hypotension
- weight loss, anorexia, nausea/vomiting, diarrhea
- abdominal, muscle, and joint pain

**primary**
- hyperpigmentation of skin and mucous membranes (e.g. palmar creases and buccal mucosa)
- dehydration, salt craving

**secondary**
- usually more chronic than primary
- pallor, normal K+ and hydration
1) Chronic insufficiency of adrenal glands: Laboratory Findings

- hyponatremia, hyperkalemia, elevated BUN/creatinine
- chronic anemia (normochromic, normocytic)
  - primary
    - low cortisol unresponsive to exogenous ACTH
    - high ACTH
    - adrenal antibodies if autoimmune etiology
  - secondary
    - low cortisol, low ACTH
    - usually normal K+, BUN/creatinine
1) Chronic insufficiency of adrenal glands:

What is Addison’s disease?
1) Chronic insufficiency of adrenal glands: Addison’s disease

Addison’s disease (also chronic adrenal insufficiency, primary adrenocortical insufficiency, hypocortisolism, and hypoadrenalism) is a rare, chronic endocrine disorder in which the adrenal glands do not produce sufficient steroid hormones (glucocorticoids and often mineralocorticoids). This is a rare condition with an estimated incidence in the developed world of 0.8 cases per 100,000 and prevalence of 4 to 11 cases per 100,000 population.
1) Chronic insufficiency of adrenal glands:

Etiology of and risk factors for Addison’s disease
1) Chronic insufficiency of adrenal glands: Addison’s disease. Etiology and risk factors

ETIOLOGY AND RISK FACTORS

- **Tuberculosis (TB):** TB is an infection which usually affects the lungs. In some cases, the infection can spread to, and gradually destroy, the adrenals.
- Other infections can sometimes affect both adrenals.
- Cancers of other parts of the body can spread and destroy the adrenals.
- Rare hereditary conditions.
- Adrenalectomy
- Autoimmune diseases: autoimmune diseases that cause the immune system to make antibodies against part or parts of the body. In autoimmune Addison's disease, you make antibodies that attach to cells in the adrenal cortex.
1) Chronic insufficiency of adrenal glands: Addison’s disease  Etiology and risk factors

- ↑glycolysis, ↓gluconeogenesis
- Dystrophic changes in tissues
- ↓protein synthesis, immunity
- ↓Na- dehydration, osmolarity, BP
- Anorexia, muscles atrophy, ↓weight, testosterone

Secondary/Tertiary Adrenal Insufficiency:
Hypothalamic or pituitary dysfunction
No mineralcorticoid defect

1) Chronic insufficiency of adrenal glands:

Clinical features of Addison’s disease
1) Chronic insufficiency of adrenal glands: Addison’s disease. Clinical features

**Chronic**

- Anorexia and weight loss (>90%)
- Tiredness
- Weakness—generalized, no particular muscle groups
- Pigmentation—generalized, but most common in light-exposed areas and areas exposed to pressure (elbows and knees, and under bras and belts); mucosa and scars acquired after onset of adrenal insufficiency
1) Chronic insufficiency of adrenal glands: Addison’s disease. Clinical features

Chronic

- Look at palmar creases in Caucasians.
- Dizziness and postural hypotension
- GI symptoms—nausea and vomiting, abdominal pain, diarrhea
- Arthralgia and myalgia
- Symptomatic hypoglycemia—rare in adults
- ↓ Axillary and pubic hair and reduced libido in women
- Pyrexia of unknown origin—rarely

1) Chronic insufficiency of adrenal glands: Addison’s disease. Clinical features
1) Chronic insufficiency of adrenal glands:

Diagnosis of Addison’s disease
1) Chronic insufficiency of adrenal glands: Addison’s disease. Diagnosis

Screening recommendations

- 2.4% of patients with a monoglandular autoimmune endocrinopathy have APS2 on subsequent follow-up.
- Functional screening is recommended every 3 years until the age of 75 years
- Serum Na⁺, K⁺, Ca²⁺, blood cell count
- TSH, free T₄
- FSH, LH, testosterone, or estradiol
- Fasting morning cortisol and glucose
1) Chronic insufficiency of adrenal glands: Addison’s disease. Diagnosis

**Screening recommendations**

- Optional: ACTH stimulation test
- If a second endocrinopathy is diagnosed, measure organ-specific autoantibodies and consider functional screening in first-degree relatives

  - Islet cells, GAD, IA2
  - TPO, TSH receptor
  - Cytochrome P450 enzymes
  - H⁺-K⁺-ATPase of the parietal cells, intrinsic factor
  - Transglutaminase, gliadin

1) Chronic insufficiency of adrenal glands: Addison’s disease. Diagnosis

CT/MRI imagine
A CT scan may reveal enlarged or calcified adrenals, suggesting an infective, hemorrhagic, or malignant diagnosis.
1) Chronic insufficiency of adrenal glands: How is Addison’s disease treated?
1) Chronic insufficiency of adrenal glands: Addison’s disease. Treatment

Maintenance therapy

Glucocorticoid replacement

- Hydrocortisone is the treatment of choice for replacement therapy, as it is reliably and predictably absorbed and allows biochemical monitoring of levels
- It is administered 3 × daily 10 mg on waking, 5 mg at midday, and 5 mg at 6 P.M
- Some patients can be managed adequately with twice-daily administration of hydrocortisone
- An alternative is prednisone 5 mg once daily
- This has the disadvantage that levels cannot be biochemically monitored, but its longer t½ may lead to better suppression of ACTH if pigmentation and markedly elevated morning ACTH levels are a problem

1) Chronic insufficiency of adrenal glands: Addison’s disease. Treatment

Mineralocorticoid replacement

- Fludrocortisone (9-flurohydrocortisone) is given at a dose of 0.1 mg daily
- Aim to avoid significant postural fall in BP (>10 mmHg)
- Lower (0.05 mg) or higher (0.2 mg) doses are required
- A dose of 40 mg hydrocortisone has the equivalent mineralocorticoid effects as 0.1 mg fludrocortisone
- Renin activity can help guide adequacy of therapy
1) Chronic insufficiency of adrenal glands: Addison’s disease. Treatment

DHEA replacement

- Dihydroepiandrosterone (DHEA) is also deficient in hypoadrenalism
- DHEA replacement (25–50 mg/day) may improve mood and well-being (as dietary supplement)
1) Chronic insufficiency of adrenal glands: Addison’s disease. Treatment

Monitoring of therapy

Clinical

- For signs of glucocorticoid excess, e.g., i weight
- BP (including postural change)
- Hypertension and edema suggest excessive mineralocorticoid replacement, whereas postural hypotension and salt craving suggest insufficient treatment
1) Chronic insufficiency of adrenal glands: Addison’s disease. Treatment

Biochemical

- Serum electrolytes
- Plasma renin activity (elevated if insufficient fludrocortisone replacement)
- Very dependent on when the last dose was taken
- Cortisol day curve to assess adequacy of treatment

Monitor ACTH levels prior to and following morning glucocorticoid replacement if the patient develops pigmentation.

If levels are elevated or rising with little suppression following glucocorticoid, obtain an MRI scan to exclude the rare possibility of pituitary hyperplasia or, very rarely, the development of a corticotrope adenoma.

2) Hyperfunction of adrenal glands: hyperaldosteronism

What causes of mineralocorticoid excess (hyperaldosteronism) do you know?
2) Hyperfunction of adrenal glands: causes of mineralocorticoid excess

- Most cases of mineralocorticoid excess are due to excess aldosterone production, which may be primary or secondary, and are typically associated with hypertension and hypokalemia.
- **Primary** hyperaldosteronism is a disorder of autonomous aldosterone hypersecretion with suppressed renin levels.
- **Secondary** hyperaldosteronism occurs when aldosterone hypersecretion occurs secondary to elevated circulating renin levels.
- This is typical of heart failure, cirrhosis, or nephrotic syndrome, but can also be due to renal artery stenosis and, occasionally, a very rare renin-producing tumor (reninoma).
2) Hyperfunction of adrenal glands: causes of mineralocorticoid excess

**Primary hyperaldosteronism**
- Conn’s syndrome (aldosterone-producing adrenal adenoma): 35%
- Bilateral adrenal hyperplasia: 60%
- Glucocorticoid remedial aldosteronism (GRA): <1%
- Aldosterone-producing adrenal carcinoma

**Secondary hyperaldosteronism** increase in aldosterone in response to activation of renin-angiotensin system
- overproduction of renin (e.g. primary reninism from renin-producing tumour - rare)
- secondary hyperreninism - due to hypoperfusion of kidneys (e.g. renal artery stenosis), or edematous states (CHF, liver cirrhosis), where arterial hypovolemia and/or hypotension is stimulus for aldosterone secretion (Bartter’s syndrome - severe secondary hyperaldosteronism without edema or hypertension (due to JGA hyperplasia)) or Renin-secreting tumor
2) Hyperfunction of adrenal glands: effects of mineralocorticoid excess

- Aldosterone causes renal sodium retention and potassium loss
- This results in expansion of body sodium content, leading to suppression of renal renin synthesis
- The direct action of aldosterone on the distal nephron causes sodium retention and loss of hydrogen and potassium ions, resulting in a hypokalemic alkalosis, although serum potassium may not be significantly reduced and may be normal in up to 50% of cases
- Aldosterone excess has pathophysiological effects on a range of other tissues, causing cardiac fibrosis, vascular endothelial dysfunction, and nephrosclerosis
2) Hyperfunction of adrenal glands: clinical features of mineralocorticoid excess

- Moderately severe hypertension occurs, which is often resistant to conventional therapy.
- There may be disproportionate left ventricular hypertrophy.
- Hypokalemia OFF diuretics.
- Hypokalemia is usually asymptomatic.
- Occasionally, patients may present with tetany, myopathy, polyuria, polydipsia, and nocturia (hypokalemic nephrogenic diabetes insipidus), paresthesias due to severe hypokalemia.
- Other symptoms may include fatigue, weakness, headaches.
2) Hyperfunction of adrenal glands: mineralocorticoid excess

What is Conn’s syndrome?
2) Hyperfunction of adrenal glands: mineralocorticoid excess. Conn’s syndrome 1.1

**Conn’s syndrome—aldosterone-producing adrenal adenoma**

- Very high levels of the enzyme aldosterone synthase are expressed in tumor tissue
- Although aldosterone production is autonomous, ACTH has a greater stimulatory effect than angiotensin II (aldosterone often displays a diurnal variation that mirrors that of cortisol), although a subtype that remain more responsive to angiotensin II has been described
- Very rarely, Conn’s adenomas may be a part of the MEN1 syndrome
2) Hyperfunction of adrenal glands: mineralocorticoid excess. Conn’s syndrome:

Imaging

Adrenal adenoma: Axial CT image in (a) shows hypodense fat containing mass (arrow) in the right adrenal. Axial CT image in (b) shows a lipid-poor adenoma in left adrenal (arrow) in a patient with Conn's syndrome.
2) Hyperfunction of adrenal glands: mineralocorticoid excess

What is Bilateral adrenal hyperplasia?
2) Hyperfunction of adrenal glands: mineralocorticoid excess. Bilateral adrenal hyperplasia

**Bilateral adrenal hyperplasia** (bilateral idiopathic hyperaldosteronism)

- This is the most common form of primary hyperaldosteronism in adults
- Hyperplasia is more commonly bilateral than unilateral and may be associated with micronodular or macronodular hyperplasia
- CT-demonstrable nodules have a prevalence of 2% in the general population, including hypertensive patients without excess aldosterone production
- The pathophysiology is not known, although aldosterone secretion is very sensitive to circulating angiotensin II
- The pathophysiology of bilateral adrenal hyperplasia is not understood; it is possible that it represents an extreme end of the spectrum of low rennin-essential hypertension
2) Hyperfunction of adrenal glands: mineralocorticoid excess

Diagnosis of mineralocorticoid excess?
2) Hyperfunction of adrenal glands: mineralocorticoid excess. Diagnosis

Screening

Indications

- Patients resistant to conventional antihypertensive medication (i.e., not controlled on three agents one of which is diuretic)
- Hypertension associated with hypokalemia (potassium < 3.7 mmol/L, irrespective of thiazide use)
- Hypertension developing before 40 years of age
- Adrenal incidentaloma
2) Hyperfunction of adrenal glands: mineralocorticoid excess. Diagnosis

Method

- False-negative and false-positive results can occur if the test is not performed under controlled circumstances
- Give oral supplements of potassium to control hypokalemia
- Stop medication that can interfere with the test using appropriate washout period
- Blood pressure (BP) can be controlled using doxazosin or verapamil (rather than other calcium antagonists)
- Measure aldosterone/renin ratio
2) Hyperfunction of adrenal glands: mineralocorticoid excess. Diagnosis

Confirmation of diagnosis

- Confirmation of autonomous aldosterone production is made by demonstrating failure to suppress aldosterone in the face of sodium/volume loading
- This can be achieved through a number of mechanisms after optimizing test conditions as described
2) Hyperfunction of adrenal glands: mineralocorticoid excess. Diagnosis

**Dietary sodium loading**

- Patients can be instructed to take a diet with high sodium content (sufficient to raise the sodium intake to 200 mmol/day for 3 days)
- If necessary, this can be achieved by adding supplemental sodium chloride tablets
- It is important to ensure that potassium is maintained during this period; potassium supplementation may also be required
- Failure to suppress 24-hour urinary aldosterone secretion at the end of this period is diagnostic of primary aldosteronism
2) Hyperfunction of adrenal glands: mineralocorticoid excess. Diagnosis

**Saline infusion test**

- Administer 2 L normal saline over 4 hours, preferably between 8 A.M. and noon.
- Measure plasma aldosterone at 0 and 4 hours.
- Aldosterone fails to suppresses to <7.5 ng/mL (7.5–10 equivocal) in 80–90% of primary aldosteronism.

**Frequently**

- This test is followed by measurements of plasma rennin activity (PRA) with upright posture and use of a diuretic (furosemide up to 80 mg).
- Low PRA under these conditions supports the diagnosis.
2) Hyperfunction of adrenal glands: mineralocorticoid excess. Diagnosis

**Captopril suppression test**
- Plasma aldosterone is measured in the sitting position, basally, and 60 minutes after captopril 25 mg.
- Inhibition of angiotensin II leads to a fall in aldosterone in patients with idiopathic hyperaldosteronism but not in Conn’s syndrome

**Fludrocortisone suppression test**
- Give fludrocortisone 100 mcg q6h for 4 days
- Measure aldosterone basally and on last day
- Aldosterone is suppressed in hyperplasia but unchanged in adenomas
2) Hyperfunction of adrenal glands: mineralocorticoid excess. Diagnosis

CT/MRI scan are of value in identifying adrenal adenomas.

That the frequency of adrenal incidentalomas rises with age and, for this reason, it is prudent to consider adrenal vein sampling in older patients (age >50) with primary aldosteronism who have an apparent solitary adenoma on scanning.

- Identifies most adenomas >5 mm diameter
- Bilateral abnormalities or tumors <1 cm in diameter require further localization procedures
- In bilateral adrenal hyperplasia, both glands can appear enlarged or normal in size
- Macronodular hyperplasia may result in identifiable nodules on imaging
- A mass >4 cm in size is suspicious of carcinoma but is unusual in Conn’s syndrome
- In essential hypertension, nodules are described...
2) Hyperfunction of adrenal glands: mineralocorticoid excess. Diagnosis

Adrenal vein sampling

- Aldosterone measurements from both adrenal veins allow a gradient between the two sides to be identified in the case of unilateral disease.
- It is the gold standard for differentiation between uni- and bilateral aldosterone production, but cannulating the right adrenal vein is technically difficult, as it drains directly into the inferior vena cava.
- Cortisol measurements must also be taken concomitantly with aldosterone to confirm successful positioning within the adrenal veins and should be more than 3× a peripheral sample (central/peripheral ratio >3).
- The aldosterone/cortisol ratio with an adenoma is >4.1.
2) Hyperfunction of adrenal glands: mineralocorticoid excess. Diagnosis

Radiolabeled iodocholesterol scanning

- This test has low sensitivity and specificity and offers no advantage over a high-resolution CT or MRI with, where necessary, adrenal vein sampling
2) Hyperfunction of adrenal glands: mineralocorticoid excess.

Treatment
2) Hyperfunction of adrenal glands: mineralocorticoid excess. Treatment

**Surgery**

- Laparoscopic adrenalectomy
- Surgery is not indicated in patients with idiopathic hyperaldosteronism, as even bilateral adrenalectomy may not cure the hypertension
- Presurgical spironolactone treatment may be used to correct potassium stores before surgery
- The BP response to treatment with spironolactone (50–400 mg/day) before surgery can be used to predict the response to surgery of patients with adenomas
- Hypertension is cured in about 70% of patients. If it persists (more likely in those with long-standing hypertension and increased age), it is more amenable to medical treatment.
- Overall, 50% become normotensive in 1 month and 70% within 1 year
2) Hyperfunction of adrenal glands: mineralocorticoid excess. Treatment

Medical treatment

- Medical therapy remains an option for patients with a solitary adrenal adenoma who are unlikely to be cured by surgery, who are unfit for operation, or who express a preference for medical management.

- The aldosterone antagonist spironolactone (50–400 mg/day) has been used successfully for many years to treat the hypertension and hypokalemia associated with bilateral adrenal hyperplasia and idiopathic hyperaldosteronism.

- There may be a delay in response of hypertension of 4–8 weeks.

- Combination with other antihypertensive agents (ACE inhibitor and calcium channel blockers) is usually required.

- Side effects are common, particularly gynecomastia and impotence in men, menstrual irregularities in women, and GI effects.
2) Hyperfunction of adrenal glands: mineralocorticoid excess. Treatment

- **Eplerenone** (50–100 mg/day) is a mineralocorticoid antagonist without antiandrogen effects and greater selectivity than that of spironolactone.
- Alternative drugs include the potassium-sparing diuretics amiloride and triamterene.
- **Amiloride** may need to be given in high dose (up to 40 mg/day) in primary aldosteronism, and monitoring of serum potassium is essential. Calcium channel antagonists may also be helpful.
- Glucocorticoid-remedial aldosteronism can be treated with low-dose **dexamethasone** (0.5 mg on going to bed). Side effects often limit therapy, and spironolactone or amiloride treatment is often preferred.
2) Hyperfunction of adrenal glands: hypercortisolism

What is Cushing’s syndrome?
Definition
2) Hyperfunction of adrenal glands (hypercortisolism) Cushing’s syndrome. Definition

Cushing’s syndrome results from chronic glucocorticoid excess (endogenous or exogenous sources)
2) Hyperfunction of adrenal glands: hypercortisolism

Etiology and Classification of Cushing’s syndrome
Etiology and Classification

**ACTH-Dependent**
- Cushing's disease (pituitary-dependent)
- Ectopic ACTH syndrome
- Ectopic CRH syndrome
- Macronodular adrenal hyperplasia
- Iatrogenic (treatment with ACTH 124)

**ACTH-Independent**
- Adrenal adenoma and carcinoma
- Primary pigmented nodular adrenal hyperplasia and Carney's syndrome.
- McCune-Albright syndrome
- Aberrant receptor expression (gastric inhibitory polypeptide, interleukin-1).
- Iatrogenic (e.g., pharmacologic doses of prednisolone, dexamethasone)

**Pseudo-Cushing's Syndromes**
- Alcoholism
- Depression
- Obesity

ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone.
2) Hyperfunction of adrenal glands: hypercortisolism

What are the main clinical features of hypercortisolism?
2) Hyperfunction of adrenal glands: hypercortisolism. Clinical Features

**general**
- truncal (centripetal) obesity, thin extremities, supraclavicular fat pads,
- posterior cervical fat ("buffalo hump"), "moon facies"
- hypertension

**skin**
- thin skin, facial plethora, hirsutism in women, wide purple striae,
- acne, easy bruising, poor wound healing, mucocutaneous candidiasis

**musculoskeletal**
- osteoporosis, pathologic fractures, avascular necrosis (AVN)
- proximal muscle weakness (more prominent in lower limbs)
Hyperfunction of adrenal glands: hypercortisolism. Clinical Features

**neuropsychiatric**
- emotional lability, depression, euphoria, frank psychosis

**gonadal dysfunction**
- oligomenorrhea / amenorrhea in women, decreased libido / impotence in men

**metabolic**
- glucose intolerance (frank diabetes less common), hyperlipidemia, polyuria, nephrocalcinosis

**ectopic ACTH production**
- hyperpigmentation, hypertension, hypokalemic metabolic alkalosis, weight loss, weakness (typical features of Cushing’s syndrome usually absent)
Pendulous abdomen

Moon face

Fat pads

Buffalo hump

Red cheeks

Dark facial hair (in women)

Thin arms and legs

Abdominal striae

Central fat deposition

Thinning of limbs

Bruising
2) Hyperfunction of adrenal glands: hypercortisolism

Diagnosis of hypercortisolism?
2) Hyperfunction of adrenal glands: hypercortisolism. Differential diagnosis

Clinical features suspicious for hypercortisolism:

- 24 hour urinary free cortisol:
  - Normal
  - < 4X increase:
    - Low dose DST to confirm diagnosis
  - > 4X increase:
    - Diagnosis of Cushing's syndrome established

Measure ACTH:

- ACTH increased:
  - MRI pituitary, inferior petrosal sinus sampling with CRF stimulation test
- ACTH decreased:
  - CT adrenal, confirmatory high-dose DST

DST = Dexamethasone Suppression Test

2) Hyperfunction of adrenal glands: hypercortisolism. Cushing’s syndrome. Diagnosis

**Diagnosis**

- Does the patient have Cushing's syndrome?
  - Circadian rhythm of plasma cortisol
  - Urinary free cortisol excretion
  - Low-dose dexamethasone suppression test

**Differential Diagnosis**

What is the cause of the Cushing's syndrome?

- Plasma ACTH
- Plasma potassium, bicarbonate
- High-dose dexamethasone suppression test
- Metyrapone test
- Corticotropin-releasing hormone
- Inferior petrosal sinus sampling
- CT, MRI scanning of pituitary, adrenals
- Scintigraphy
- Tumor markers

ACTH, adrenocorticotropic hormone; CT, computed tomography; MRI, magnetic resonance imaging.
Circadian Rhythm of Plasma Cortisol 2.6

- In normal subjects, plasma cortisol levels are at their highest early in the morning and reach a nadir (<50 nmol/L [<2 µg/dL] in a nonstressed subject) at about midnight.
- This circadian rhythm is lost in patients with Cushing’s syndrome: the 9 a.m. plasma cortisol is normal but nocturnal levels are raised.
- Midnight cortisol level greater than 200 nmol/L (>7.5 µg/dL) indicates Cushing’s syndrome.
- Patients should be hospitalized for 24 to 48 hours before the midnight cortisol level is measured.

Figure 6.5 Typical diurnal variations in serum cortisol. Levels peak in the early morning and trough in the evening. In Cushing syndrome, diurnal variations are lost.
2) Hyperfunction of adrenal glands: hypercortisolism. Cushing’s syndrome. Diagnosis

Urinary Free Cortisol Excretion

- Normal values are less than 220 to 330 nmol/24 hours (80 to 120 µg/24 hours), depending on the assay used
- Patients should make two or three complete consecutive collections to account for patient error in collecting samples and for episodic cortisol secretion, notably from adrenal adenomas
2) Hyperfunction of adrenal glands: hypercortisolism. Cushing’s syndrome. Diagnosis

Low-Dose Overnight Dexamethasone Suppression Tests

- In normal subjects, the administration of a supra-physiologic dose of glucocorticoid results in suppression of ACTH and cortisol secretion.
- In Cushing’s syndrome of whatever cause, there is a failure of this suppression when low doses of the synthetic glucocorticoid dexamethasone are given.
- 1 mg of dexamethasone is given at mid-night or 0.5 mg every 6 hours. A normal response is a plasma cortisol level of less than 140 nmol/L (<5 µg/dL) between 8 and 9 a.m. the following morning.
Hyperfunction of adrenal glands: hypercortisolism. Cushing’s syndrome. Imaging

Computed Tomographic and Magnetic Resonance Imaging Scanning of Pituitary and Adrenals

Pituitary MRI is the investigation of choice when the biochemical tests suggest Cushing's disease.

Abdominal CT scans revealed a left adrenal oval-shaped mass (red X) in coronal (c) and axial images (d).

Bone abnormalities in Cushing’s disease

Aseptic necrosis of the right humeral head in a 43-year-old woman with Cushing’s disease of about 8 months’ duration.

Aseptic necrosis of the right femoral head in a 24-year-old woman with Cushing’s disease of about 4 years’ duration. The arrows indicate the crescent subchondral radiolucency, best seen in this lateral view.

Diffuse osteoporosis, vertebral collapse, and subchondral sclerosis in the same patient.

Rib fracture in a 38-year-old man with Cushing’s disease.
Hyperfunction of adrenal glands: hypercortisolism. Treatment: general approaches

**Pituitary**
- transsphenoidal resection, with glucocorticoid supplement peri- and post-operatively
- irradiation: only 50% effective, with significant risk of hypopituitarism

**Adrenal**
- adenoma: unilateral adrenalectomy (curative)
- carcinoma: palliative (frequent metastases, very poor prognosis)

Adjuvant chemotherapy often not useful

**Ectopic ACTH tumour** - usually bronchogenic cancer (a paraneoplastic syndrome)
- chemotherapy/radiation for primary tumour
- agents blocking adrenal steroid synthesis: metyrapone or ketoconazole
- poor prognosis
2) Hyperfunction of adrenal glands hypercortisolism

Options of treatment in case of Cushing syndrome?

From what to start?
2) Hyperfunction of adrenal glands: hypercortisolism. Cushing's Syndrome. Treatment

Adrenal Causes

- adrenal adenomas should be removed by unilateral adrenalectomy
- suboptimal replacement therapy with dexamethasone at 0.5 mg in the morning, with intermittent measurement of morning plasma cortisol before taking dexamethasone till 180 nmol/L (6 µg/dL)
- patients should carry Steroid Alert card and increase their dose of replacement therapy in the event of an intercurrent illness
2) Hyperfunction of adrenal glands: hypercortisolism. Cushing's Syndrome. Treatment

Pituitary-Dependent Cushing's Syndrome

- selective removal of a pituitary microadenoma
- postoperatively, hydrocortisone can be withdrawn to maintenance replacement doses, usually within 3 to 7 days
- on day 5 postoperatively, plasma cortisol should be measured at 9 AM with the patient having omitted hydrocortisone for 24 hours
- plasma cortisol levels are less than 30 nmol/L (1 µg/dL) postoperatively - glucocorticoid replacement therapy
2) Hyperfunction of adrenal glands: hypercortisolism

If surgical treatment is not possible or contraindicated what to do?
2) Hyperfunction of adrenal glands: hypercortisolism. Cushing's Syndrome. Treatment

- **Metyrapone** - inhibits 11-hydroxylase to lower cortisol concentrations prior to definitive therapy or while awaiting benefit from pituitary radiation from 250 mg twice daily to 1.5 g every 6 hours

- **Aminoglutethimide** - blocks earlier enzymes in the steroidogenic pathway and thus affects the secretion of steroids - in doses of 1.5 to 3 g daily (start with 250 mg every 8 hours)

- **Ketoconazole** - blocks a variety of steroidogenic cytochrome P450-dependent enzymes and thus lowers plasma cortisol levels - 400 to 800 mg daily
3) Acute insufficiency of adrenal glands (acute adrenal crisis)

What is Adrenal crisis?
Adrenal crisis etiology
3) Acute insufficiency of adrenal glands (acute adrenal crisis). Etiology

Inability to secrete increased cortisol, ACTH in response to stress (e.g. infection, dehydration, surgery)

- Acute decompensation of Addison’s disease due to infections, surgery etc
- 2-sided adrenalectomy due to Cushing disease
- Aplasia of adrenal glands
- Mts of tumor to adrenal gland
- Dysfunction of adrenal cortex due to severe stress
- Central nervous system disorders: tumors, meningitis, encephalitis etc.
- Waterhouse – Fridrecesen syndrome – acute adrenal crisis due to hemorrhage
3) Acute insufficiency of adrenal glands (acute adrenal crisis)

Clinical features of acute adrenal crisis
3) Acute insufficiency of adrenal glands: Adrenal crisis. Clinical features

- Shock
- Hypotension (often not responding to measures such as inotropic support)
- Abdominal pain (may present as acute abdomen)
- Unexplained fever
- Often precipitated by major stress such as severe bacterial infection,
- major surgery, unabsorbed glucocorticoid medication due to vomiting
- Occasionally occurs due to bilateral adrenal infarction
3) Acute insufficiency of adrenal glands: Adrenal crisis. Clinical features
3) Acute insufficiency of adrenal glands: Adrenal crisis. Clinical features (Clinical forms)

1. Cardio-vascular
   - Collapse
   - Hypotension
   - Cyanosis
   - Hypothermia
   - Cardiac failure

2. gastro-intestinal
   - Nausea
   - Vomiting
   - Acute abdominal pain
   - Diarrhea

3. Neurogenic
   - Brain edema
   - Astenia
   - Depression
   - Seizure
   - Catatonia
3) Acute insufficiency of adrenal glands (acute adrenal crisis)

How you will treat it?
3) Acute insufficiency of adrenal glands: Adrenal crisis. Treatment

Emergency management of acute adrenal insufficiency

- This is a life-threatening emergency and should be treated if there is strong clinical suspicion, rather than waiting for confirmatory test results.
- Blood should be taken for urgent analysis of electrolytes and glucose, in addition to cortisol and ACTH.
3) Acute insufficiency of adrenal glands: Adrenal crisis. Treatment

**Fluids**

- Large volumes of 0.9% saline may be required to reverse the volume depletion and sodium deficiency
- Several liters may be required in the first 24–48 hours, but caution should be exercised where there has been chronic hyponatremia; in this circumstance rapid correction of the deficit exposes the patient to risk of central pontine myelinolysis
- If plasma sodium is <120 mmol/L at presentation, aim to correct this by no more than 10mmol/L in the first 24 hours
Acute insufficiency of adrenal glands: Adrenal crisis. Treatment

Hydrocortisone

- A bolus dose of 100 mg hydrocortisone is administered intravenously
- Hydrocortisone 100 mg IM is then continued 6-hourly for 24–48 hours or until the patient can take oral therapy
- Double replacement dose hydrocortisone (20, 10, and 10 mg orally) can then be instituted until well
- This traditional regimen causes supraphysiological replacement, and some authors suggest lower doses, e.g., 150 mg IV/24 hours
3) Acute insufficiency of adrenal glands: Adrenal crisis. Treatment

Glucose supplementation

- Occasionally, this is required because of risk of hypoglycemia (low glycogen stores in the liver as a result of glucocorticoid deficiency)

Investigate and treat precipitant

- This is often infection

Monitoring treatment

- Monitor electrolytes, glucose, and urea
4) Hormonally active adrenal tumors: Pheochromocytoma

What is Pheochromocytoma?
4) Hormonally active adrenal tumors

Pheochromocytomas

- **Pheochromocytomas** are tumors of neuroectodermal origin arising from chromaffin cells.
- The name pheochromocytoma, proposed by Pick in 1912, comes from the Greek words *phaios* ("dusky") and *chroma* ("color"); it refers to the staining that occurs when the tumors are treated with chromium salts.
- The first diagnosis of pheochromocytoma was made in 1886 by Frankel, who found bilateral tumors of the adrenal gland at autopsy in an 18-year-old girl who had died suddenly.
4) Hormonally active adrenal tumors
Pheochromocytomas. Key features

- rare tumour arising from chromaffin cells of the sympathetic system
- most commonly a single tumour of adrenal medulla
- 10% extra-adrenal, 10% multiple tumours, 10% malignant, 10% familial
- tumour not innervated but via unknown mechanism, able to synthesize and release catecholamines
- cases sporadic or part of MEN (Multiple Endocrine Neoplasia)
- rare cause of hypertension (< 0.1% of all hypertensives)
- curable if recognized and properly treated, but fatal if not
Does a pheochromocytoma tumour always occur in the adrenal gland?
4) Hormonally active adrenal tumors
Pheochromocytomas. Localizations

- No
- Pheochromocytomas typically arise in about 80% to 85% of cases from adrenal medullary chromaffin tissue (also designated adrenal paragangliomas) and in about 15% to 20% of cases from extra-adrenal chromaffin tissues
- Those arising from extra-adrenal chromaffin tissue are commonly referred to as paragangliomas
- Extra-adrenal pheochromocytomas arise mainly from chromaffin tissue adjacent to sympathetic ganglia in the abdomen, less commonly from the pelvis, and rarely from the mediastinum
4) Hormonally active adrenal tumors: Pheochromocytoma

What clinical signs would you look for during physical examination?
4) Hormonally active adrenal tumors

Pheochromocytoma. Clinical signs

- symptoms are often paroxysmal, may be triggered by stress, exertion, certain foods
- hallmark is paroxysmal or sustained HTN (sustained HTN more common, present between attacks in 60% of patients)
- classic triad: “pounding” headache, palpitations, diaphoresis
- others: tremor, anxiety, chest or abdominal pain, nausea / vomiting, weight loss, pallor, fever, tremor, tachyarrhythmias, pulmonary edema, diabetes mellitus
4) Hormonally active adrenal tumors: Pheochromocytoma

What test would you request?
4) Hormonally active adrenal tumors

Pheochromocytoma. Diagnosis

- Expert recommendations for initial biochemical testing from the International Symposium on Pheochromocytoma include measurements of fractionated metanephrines in urine or plasma, or both, as available
- Three 24-h urine collections for catecholamine and metanephrine measurement
4) Hormonally active adrenal tumors
Pheochromocytoma. Diagnosis

**Catecholamine Testing**

- A fractionated plasma free metanephrine level may be measured in a standard venipuncture sample, drawn about 15–20 minutes after intravenous catheter insertion.
- Due to the episodic nature of the disease, plasma levels of catecholamines can be normal and, therefore, measurement of these hormones in the urine is more reliable (two to three collections are necessary).
- Perform a 24-hour urine collection for creatinine, total catecholamines, vanillylmandelic acid, and metanephrines. Measure creatinine in all collections of urine to ensure adequacy of the collection.
4) Hormonally active adrenal tumors
Pheochromocytoma. Diagnosis

- The collection container should be dark and acidified and should be kept cold to avoid degradation of the catecholamine.
- Optimally, collect urine during or immediately after a crisis. Although dopamine is a major catecholamine, measurement of dopamine levels in 24-hour urine is not useful, because most urinary dopamine is derived from renal extraction.
4) Hormonally active adrenal tumors

What other blood test(s) may help you to confirm your suspicion?
4) Hormonally active adrenal tumors

Pheochromocytoma. Other blood tests

- The clonidine suppression test - when the suspicion of pheochromocytoma is high but the basal catecholamine levels are not diagnostic, a decrease in basal plasma catecholamines by 50% or less than 3 nmol/L (500 pg/mL) is expected 2 to 3 hours after 0.3 mg of clonidine is administered.

- Clonidine is a centrally acting α2-adrenergic agonist that suppresses central sympathetic nervous outflow; this normally results in lowered levels of plasma catecholamines in patients without pheochromocytoma but no change in those with the tumor.
4) Hormonally active adrenal tumors
Pheochromocytoma. Other blood tests

- Blood is drawn for plasma catecholamines before and 3 hours after the oral administration of clonidine 0.3 mg/70 kg of body weight
- NANETS guidelines recommend clonidine suppression testing when plasma metanephrine values are less than 4-fold above the upper reference limit
- The clonidine suppression test is unreliable in patients with normal or only mildly increased plasma catecholamine levels
- In such patients, normal suppression of plasma norepinephrine may occur after administration of clonidine despite the presence of a pheochromocytoma
4) Hormonally active adrenal tumors

Instrumental Diagnosis of Pheochromocytoma
**CT Scanning**

Abdominal CT scanning has an accuracy of 85-95% for detecting adrenal masses with a spatial resolution of 1 cm or greater but is less accurate for lesions smaller than 1 cm.

**MRI**

is preferred for detection of pheochromocytoma in children and in pregnant or lactating women. MRI has a reported sensitivity of up to 100% in detecting adrenal pheochromocytomas, does not require contrast, and does not expose the patient to ionizing radiation.

A 53-year-old man with uncontrolled hypertension and catecholamine hypersecretion, suspected for pheochromocytoma. 123I-MIBG composite (A) anterior and (B) posterior whole-body images at 24 hours postinjection show focal intense activity in the region of the left adrenal gland (arrow).

A left adrenal pheochromocytoma with intense 123I-MIBG uptake (arrowheads). There is also pre-aortic soft tissue nodule with intense 123I-MIBG uptake (arrows) on the SPECT/CT that may represent an extraadrenal paraganglioma or less likely a metastatic retroperitoneal lymph node indicating malignant disease.

**Functional Imaging Scintigraphy**

is reserved for cases in which a pheochromocytoma is confirmed biochemically but CT scanning or MRI does not show a tumor.
4) Hormonally active adrenal tumors

How is Pheochromocytoma treated?
The patient is found to have a large left adrenal tumour measuring 5 cm in diameter.

The surgeon would like to immediately remove the tumour

Do you agree?

No, because a surgical procedure in a patient with a pheochromocytoma may precipitate a hypertensive crisis.
4) Hormonally active adrenal tumors
Pheochromocytoma. Treatment

- Surgical intervention in patients with pheochromocytomas or hormonally functional parangangliomas should in all cases only be performed after preoperative blockade of effects of catecholamines, ideally with alpha-adrenoreceptor blockers (e.g., phenoxybenzamine) administered for 7 to 14 days before surgery to normalize blood pressure.
Proposed algorithm for the preoperative treatment of patients with pheochromocytoma. 2.3

Start alpha blockade with phenoxybenzamine 10–14 days preoperatively to allow for expansion of blood volume. The patient should undergo volume expansion with isotonic sodium chloride solution. Encourage liberal salt intake. Initiate a beta blocker only after adequate alpha blockade (usually, 2 days). Administer the last doses of oral alpha and beta blockers on the morning of surgery.
Control of postoperative hypotension

The volume of fluid required is often large (0.5 to 1.5 times the patient’s total blood volume) during the first 24 to 48 hours after removal of the tumor.

This is because the half-lives of both metyrosine and phenoxybenzamine are approximately 12 hours, and thus it takes nearly three half-lives or 36 hours for the sympathetic nervous system to resume autoregulation.

When this occurs, renal output begins to increase, and blood pressure and heart rate remain stable.

Postoperative hypertension may mean that some tumor tissue was not resected.
4) Hormonally active adrenal tumors
Pheochromocytoma. Clinical case

Omar, who is 26 years old, is seen by his GP because of recurrent headaches and generally feeling unwell. His blood pressure was found to be elevated at 195/100. The patient tells you that for the past 6 months, he has been suffering from increased sweating and heat intolerance, severe headaches and episodes of palpitations associated with pallor.
From the history, what would you like to rule out as a cause for this patient’s hypertension?

4) Hormonally active adrenal tumors

Pheochromocytoma. Clinical case
4) Hormonally active adrenal tumors

Pheochromocytoma. Clinical case

- Clinical findings such as hypertension, headache, unusual sweating, frequent arrhythmias, and the presence of pallor during hypertensive episodes (so-called “spells”) are highly suggestive of pheochromocytoma
Although headache, palpitations, and sweating are nonspecific symptoms, their presence in patients with hypertension should arouse immediate suspicion for a pheochromocytoma because this triad constitutes the most commonly encountered symptoms in patients with a pheochromocytoma
Clinical Endocrinology’ Tests
A 43 year old female patient was delivered to the hospital in grave condition. She suffers from Addison’s disease. The patient had been regularly taking prednisolone but a week before she stopped taking this drug. Objectively: sopor, skin and visible mucous membranes are pigmented, skin and muscle turgor is lowered. Heart sounds are muffled, rapid. AP- 60/40 mm Hg, heart rate - 96/min. In blood: Na-120 millimole/l, K- 5,8 micromole/l. Development of this complication is primarily caused by the deficit of the following hormone:

- A. Cortisol
- B. Corticotropin (ACTH)
- C. Adrenaline
- D. Noradrenaline
- E. Adrostendion
A 26-year-old patient complains about considerable muscle weakness, dizziness, extended abdominal pain, nausea and vomiting giving no relief. The disease has been gradually developing within 6 months. There was progress of general weakness, skin darkening. The patient fell into grave condition after an ARD: there appeared abdominal pain and frequent vomiting. Objectively: the skin is dry with diffuse pigmentation. Heart sounds are significantly weakened, heart rate - 60/min, AP - 80/40 mm Hg. The abdomen is slightly painful in the epigastrial region. In blood: WBCs - 8, 1 · 109/l, glucose - 3,0 millimole/l. What is the most likely diagnosis?

- A. Chronic adrenal insufficiency. Addisonian crisis
- B. Acute pancreatitis
- C. Toxic infectious shock
- D. Acute food poisoning
- E. Acute cholecystitis
After having the flu, a 39-year-old male patient with a history of Addison’s disease developed a condition manifested by weakness, depression, nausea, vomiting, diarrhea, hypoglycemia. AP-75/50 mm Hg.

Blood test results: low corticosterone and cortisol, 13-oxycorticosteroids, 17-oxycorticosteroids levels. What condition developed in the patient?

- A. Acute adrenal insufficiency
- B. Acute gastritis
- C. Acute enterocolitis
- D. Collapse
- E. Diabetes mellitus
Test 4

After a holiday in the Crimea, a 49-year-old male patient with a history of lung tuberculosis felt increased weakness, periodic dizziness, easing bowel movements with abdominal pain, the need for additional salting his meals. The patient has noted that his condition improves after some sweet tea and validol taken sublingually. Objectively: there is an intense darkening of skin, AP 70/50 mm Hg, glycemia is 3.0 mmol/l. What is the possible cause of health deterioration:

- A. Chronic adrenal insufficiency
- B. Diabetes mellitus
- C. Coronary artery disease
- D. Chronic pancreatitis
- E. Pulmonary tuberculosis
A 32-year-old female complains of dizziness, headache, palpitation, tremor. For the last several months she has been under outpatient observation for the increased arterial pressure. Since recently such attacks have become more frequent and severe. Objectively: skin is covered with clammy sweat, tremor of the extremities is present. HR - 110/min, AP - 220/140 mmHg. Heart sounds are muffled. Blood test results: WBCs - 9,8·10⁹/l, ESR - 22 mm/h. Blood glucose - 9,8 millimole/l. What disease is the most likely cause of this crisis?

- A. Pheochromocytoma
- B. Essential hypertension
- C. Preeclampsia
- D. Primary hyperaldosteronism
- E. Diabetic glomerulosclerosis
Recommended literature

- Oxford American Handbook of Endocrinology and Diabetes
  Boris Draznin, MD, PhD, Sol Epstein, MD (2011).
  Dayan CM, Daniels GH (1996).